REMARKS

Claims 1-2, 4-6, 6-8, 10-12, 17, 21-24, 31-32, 35-37, 82-90, 93-104 are pending and rejected. Claims 25-28, 33-34, 38-58 and 60-81 are withdrawn. Support for reducing the risk or delaying the outset as recited in claim 82 is provided at e.g., p. 27, line 14. No claim amendment should be construed as acquiescence in any ground of rejection or a reduction of claim scope. Lack of comment on any of the Examiner's remarks should not be construed as acquiescence therewith.

¶6. Claims 82-90, 93-102 and 104 stand rejected on the basis that the specification is allegedly not enabling for prophylaxis of disease, as claimed. The rejection is based in part on an alleged lack of working examples showing complete elimination of risk of disease. The Examiner also alleges that the PDAPP mouse model does not realistically reflect physiology in a normal asymptomatic subject. The Examiner further alleges that it would not be desirable to decrease levels of Aβ in a normal subject based on alleged teaching of Liu that Aβ has an important physiological role in normal mammals and on alleged teaching of Perez that the precursor of Aβ has such a role.

Applicant's position has been stated in the previous response and is maintained. Nevertheless, applicant understands that the rejection might be overcome by use of alternative terminology (reducing risk or delaying outset of disease) in place of prophylaxis. Such an amendment has been made for purposes of expediting prosecution.

¶¶7-9. The claims stand rejected for alleged obviousness-type double patenting over several US Patents or applications. Applicant proposes the issues be held in abeyance until indication of allowability in the present case. Applicant maintains their offer to submit a terminal disclaimer over the cited patents if the claims are allowed in their current form.

¶10. Claims 1-2, 4, 6-8, 10-12, 17, 21-24, 31-32, 35-37, 82-90 and 93-104 stand provisionally rejected for obviousness-type double patenting over US Application No.

10/828,548 in view of Becker. The '548 application is alleged to teach methods of treatment with 10D5, an antibody having IgG1 isotype and Becker is alleged to teach humanization of antibodies. This rejection is respectfully traversed. As discussed in more detail below in connection with the rejection under 35 §USC 103, the mouse IgG1 isotype of the 10D5 antibody is the equivalent of human IgG4 not human IgG1. Thus, if an artisan were to humanize the 10D5 antibody with a view to preserving as closely as possible its mouse isotype in the context of a human constant region, the artisan would have selected human IgG4. Thus, the combination of references teaches away from the claimed human IgG1 isotype.

¶11. Claims 1, 2, 4, 10-12, 22-24, 31-32, 36, 82-84, 88-90, 95-99, 101 and 103-104 stand rejected as allegedly obvious over Becker in view of Kuby and Adair. Becker is alleged to teach treatment of Alzheimer's disease with antibodies to Aβ, Kuby is alleged to teach different isotypes of human antibodies, and Adair is alleged to teach that antibodies of human IgG1 isotype bind ICAM-1 more strongly than other isotypes. The Examiner alleges that it would have been obvious to use humanized antibodies of the IgG1 isotype in Becker's methods in view of Becker's teaching that treatment with antibodies is efficacious, Adair's teaching that IgG1 antibodies bind to antigens very well and Kuby's teaching that the properties of specific isotypes depend on the structure of the constant region not the variable region.

Applicant has previously explained how the Examiner's apparent inference from Adair and Kuby that human IgG1 antibodies generally have higher affinities than other isotypes is incorrect. In brief, Kuby says nothing about affinity depending on isotype, Adair provides a single example of an antibody affinity depending on isotype, which he characterizes as an unexpected result, and others have reported that antibody affinity does not depend on isotype.

The Examiner disagrees alleging that the artisan would clearly have understood that Adair's unexpected observation for a single antibody would be generalizable to all antibodies. This position is based on Adair's attributing the variation between isotypes to differences in flexibility of the hinge affecting avidity. However, Adair's explanation for the isotype-dependent binding affinity of his antibody is merely speculation as is the Examiner's generalization that the artisan would have clearly understand that Adair's unexpected result for a

single antibody was generalizable to every antibody. The record is devoid of any evidence that any subsequent literature has attributed any significance much less a generalizable rule to Adair's isolated observation. Moreover, Adair never asserts that his speculation regarding his particular ICAM-1 antibody is generalizable to all other antibodies binding to other antigens. Avidity is the result of a single antibody forming multiple bonds with the same antigen. Although flexibility of the hinge region might be one factor involved in the determining whether such bonds can form, the existence of and spacing of a repeated epitopes on the antigen to provide sites for multiple bonds is likely to be another. In this connection, ICAM-1, the antigen to which Adair's antibody binds is large protein having five extracellular immunoglobulin-like repeats (Staunton, Cell 52(6):925-33 (1988)) in contrast to Aβ, which is a short peptide of about 40 amino acids lacking repeat domains. (Cite 1093, cited in Supplemental IDS submitted on 08/07/2008.) Because avidity effects are likely to depend on the existence of and spacing of a repeat epitope in the same antigen, an observation for one antibody binding to a epitope on ICAM-1 would not have been generalized to every other antibody, and particularly not to an antibody binding to Aβ.

The Examiner dismisses the references providing examples in which antibody affinity does not dependent on isotype as not teaching away from the use of an IgG1 isotype. Although the references might not teach away from human IgG1 they do show the incorrectness of the Examiner's assumption that the artisan would have generalized Adair's single example to every other antibody. The simple fact that the experiments were performed and no surprise was expressed that different isotypes had about the same affinity shows that those in the field were not aware of a general rule established by Adair that human IgG1 isotype has higher affinity than other isotypes. Furthermore, even if after the present filing date, the references also show that if an artisan were to have attempted to compare isotypes in the context of an antibody to Aβ, it would have been unpredictable whether there would have been significant variation between isotypes or if so, which antibody would have had the highest affinity.

The Examiner also alleges that his determination of obviousness is consistent with the principles of KSR in that it involves choosing from a finite number of identified predictable solutions, that is, selecting one of four IgG isotypes, with IgG1 being the most abundant isotype

in human sera. The present facts and circumstances are, however, entirely different from KSR. KSR involved the combination of an adjustable foot pedal and an electronic sensor. Both the adjustable foot pedal and electronic sensor were individually in commercial use and in combination both parts performed exactly the same predictable functions as they did individually, that is, transmitting a signal from the driver's foot to the engine of a car. By contrast, the treatment or prophylaxis of Alzheimer's disease, a serious, widespread and hitherto largely untreated disease, was regarded as highly unpredictable as evidenced by the exclamations of surprise from third parties on learning of the work disclosed in the present application.

> While the amyloid hypothesis has offered drug researchers a number of obvious targets and strategies, it also led to *the most surprising attempt to thwart AD.* In the late 1990's, long after his colleagues at Elan had tested their most promising compounds, Schenk suggested injecting a few mice with beta amyloid itself. His goal was to raise an antibody or other immune response against plaques. "No one thought it would work. Even after the experiment was done, the results weren't analyzed for a while," recalls Schenk.
>
> The results were stunning. The immunization slowed or preventing the development of beta-amyloid plaques in young mice and even wiped away preexisting ones in older mice. *The episode illustrates how one person's idea can change the direction of a company or a field.* "Dale was really brave," says John Trojanowski of the University of Pennsylvania School of Medicine in Philadelphia.
>
> *How does big pharma react when a disease-treating strategy such as the Elan vaccine comes out of the blue?*
>
> Travis, Science, 309, 731-734 (2005) (emphasis supplied) (cite no. 1038, cited in Supplemental IDS submitted on 04/16/2007).
>
> This is the first time that anyone has stopped the development of amyloid plaques in a mouse model of Alzheimer's... This is a major step forward. If it does work, it would stand as one of the great scientific success stories of all time.

> Marcell Morrison-Bogorad of the National Institute on Aging in Science News Online 156, 2 (July 10, 1999), (cite no. 839, cited in Supplemental IDS submitted on 04/16/2007).
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> It's wild and amazing....Almost all scientists would have dismissed the immunization approach... because of the dogma that the so-called blood-brain barrier keeps circulating antibodies out of the brain.
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> Sangram S. Sisodia, University of Chicago, as quoted in Science News Online 156, 2 (July 10, 1999), (cite no. 839, cited in Supplemental IDS submitted on 04/16/2007).
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> Schenk surprised the Alzheimer's research community in June 1999 when he announced the vaccine worked to stop and even somewhat reverse the disease in mice. These mice were observed to perform better on memory tests.
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> Free Press, July 23, 2001, (cite no. 840, cited in Supplemental IDS submitted on 04/16/2007).
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> The idea was revolutionary because most Alzheimer's experts believe that the inflammation provoked by amyloid plaques contributes to the destruction of brain cells. Many predicted that stirring up the immune system with a vaccine would only make the disease worse....Schenk's 1999 paper on the Elan vaccine created a sensation not least because the unexpected findings suggested that vaccines might be helpful in disorders where no one had thought of using them. His results have since been confirmed by other researchers.
>
> Washington Post, May 8, 2001, (cite no. 841, cited in Supplemental IDS submitted on 04/16/2007)

Further, the inventor of the present application, Dr. Dale Schenk, was awarded the 2001 Potamkin Prize of the American Academy of Neurology (see cite no. 837 cited in the Supplemental IDS filed 04/16/2007). This is an internationally recognized award for scientists who have made a significant contribution to the prevention or treatment of neurological disease. Roger Rosenberg, M.D., former president of the American Academy of Neurology, said that Dr. Schenk's research was recognized for the "quantum leap in thinking and implementation that it

provides." Dr. Rosenberg added: "So important and unexpected are these findings that we awarded Dr. Schenk the Potamkin Prize as a solo award, recognition previously accorded only to Dr. Robert Terry and Dr. Stanley Prusiner" (both of whom subsequently won the Nobel Prize).

Although the above comments were made primarily with reference to active immunotherapy rather than passive immunotherapy as claimed, they illustrate more generally that the first demonstration of disease modification in an animal model by an immunotherapeutic approach was regarded as dramatic and surprising news that changed the direction of the field. The above comments show that disinterested observers were not convinced of immunotherapy as a viable treatment of Alzheimer's disease until publication of the first results showing disease modification in an animal model in the present inventor's work in mid-1999.

Although the references cited by applicant showing surprise at the breakthrough nature of the present inventor's work do not specifically discuss the references cited by the Examiner in the present office action, it cannot reasonably be expected that evidence of this type (spontaneous comments by neutral experts unconnected with the prosecution of the application) would discuss the precise rejections later made by a patent examiner. The evidence is of value because it includes the unbiased opinions of experts working in the field at the relevant time and is free of the distortions of hindsight when the art is viewed for the first time only after acquiring knowledge that the claimed methods are in fact successful. Moreover, the references do indicate what it was about the present inventor's work that was regarded as dramatic, surprising and changing the direction of the field notwithstanding references such as Becker and Adair. That is, the present inventor's work represents the first demonstration of modification of Alzheimer's disease in an animal model.

Whether the cited art provided a reasonable expectation of success is a different issue than whether the cited art references are themselves enabling. A prophetic reference describing a proposed method can work exactly as described (i.e., be enabling) but also be unpredictable because of the nature of the subject matter and because no data are provided to show that the method works. A reference that is itself unpredictable does not render future developments in the field any more predictable unless and until the source of unpredictability is removed. Thus, applicant's remarks concerning the lack of reasonable expectation of success do

not require the Examiner to find a prophetic reference such as Becker to lack enablement, but simply to consider what predictive value such a reference would have had to the skilled person at the effective filing date of the application without any supportive data. The above excerpts show that disinterested observers in the field were not convinced of immunotherapy as a viable treatment of Alzheimer' s disease until publication of the first results showing disease modification in an animal model. Thus, a reference lacking such results would not have been viewed as being reasonably predictive of success.

Instead of considering Becker from the perspective of the skilled person not knowing whether the methods discussed in the reference would be successful in treatment of Alzheimer's disease, the Examiner instead appears to be viewing the reference from an artificial perspective in which it is presumed that the methods had worked and all unpredictability is removed. The source of this presumption is apparently MPEP 2121, which provides that "when the reference relied on expressly anticipates or makes obvious *all of the elements of the claimed invention,* the reference is presumed to be operable (emphasis supplied)." Such a presumption is inapplicable here because no single reference is cited as disclosing or rendering obvious all elements of the invention. More fundamentally, however, operability, which equates to enablement, is not the same as predictability for the reasons discussed above.

Becker's discussion of antibodies is also far removed from that of a foot peddle or sensor of KSR. Whereas both an adjustable foot peddle and electronic sensor were in commercial use in the KSR case, Becker does not provide even an example of an antibody, much less experimental evidence that the antibody could be used. Adair discusses an example of an antibody with human IgG1 isotype for binding ICAM-1. However, it was unpredictable whether similar considerations in selection of isotype would apply to an antibody to Aβ for treatment in Alzheimer's disease. As discussed in the Washington Post article excerpted above, concern that Alzheimer's disease was at least in part mediated by inflammation would have tended to teach away from the use of human IgG1 in that this isotype has the strongest interaction with phagocytic cells and complement. Finally, that human IgG1 isotype is the most common isotype in human sera would have been irrelevant to the selection of isotype in a humanized antibody

because the recombinant techniques used in making such antibodies allow selection of any isotype irrespective of abundance in human sera.

In sum, the present claims are distinguished from KSR in the nature of what is being combined and particularly in the predictability or lack of thereof of the combination.

The teachings of KSR regarding hindsight are, however relevant. "A factfinder should be aware ....of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning," *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1397 (2007). Here several of the arguments of the Examiner do appear to rely on hindsight bias and ex post reasoning. First, the Examiner generalizes an unexpected finding of one antibody to apply to all antibodies without any support in the literature. Second, the Examiner simply assumes that Adair's speculation about affinity would be the determinative factor in selection of the isotype to the exclusion of considerations as to whether complement or phagocytic activity would have exacerbated an inflammatory basis of Alzheimer's disease as discussed in the Washington Post article. Third, the Examiner's simply presumes from Becker that treatment of Alzheimer's disease with antibodies would be successful without any supporting evidence. Such a presumption is contrary to the views of disinterested experts in the field as evidenced by the excerpts above, and not compelled by MPEP 2121. Finally, the Examiner's position does not take into account that his alternative ground of obviousness based on Walker would result in selection of a different isotype (see discussion below). In short, the case of obviousness shows hindsight by selective reliance on only part of the art, overgeneralization of another aspect of the art and unsupported presumptions contrary to the views of those in the field at the relevant time.

For these reasons, it is respectfully submitted that the claimed methods of treating Alzheimer's disease were not obvious and the rejection should be withdrawn.

Claims 103 and 104 are submitted to be further distinguished notwithstanding the Examiner's allegations of inherency. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Here, the Examiner alleges that because claims 103 and 104 recite functional properties, he can simply assume that

these properties are inherent in Becker's antibodies. However, the Examiner has provided no reasoning to explain how an antibody that specifically binds Aβ in beta-sheet form *without* binding in alpha helical form or vice versa (as discussed) by Becker necessarily binds Aβ in *both* aggregated and dissociated forms as specified in claims 103 and 104.

¶¶12-21. All of the remaining art rejections are also premised on the allegation that the combination of Kuby and Adair would have rendered obvious the selection of a human IgG1 isotype in the claimed methods. The distinctions discussed above are thus equally applicable.

¶22. Claims 1-2, 4, 10-12, 24l 31-32, 36, 82-84, 88-90, 97-99, 101 and 103-104 stand rejected as allegedly obvious over Becker in view of Walker, Hanan and Majocha. Becker is applied as above. Walker is alleged to teach diagnostic imaging with a 10D5 antibody of IgG1 isotype. Hanan is alleged to teach using a 10D5 antibody for inhibiting in vitro aggregation. Majocha is alleged to teach diagnostic methods by which the artisan would have immediately understood that antibodies are able to cross the blood brain barrier. The Examiner acknowledges that a similar rejection was made previously in prosecution and distinguished in an appeal brief (to which the Patent Office never responded) but is re-raising this issue in part because the Examiner cannot find any teaching in the Paul reference cited in the appeal brief that mouse IgG1 is the equivalent of anything other than IgG1 in humans.

In reply, applicant was referring to the equivalence of several functional properties between human IgG1 and mouse IgG2a reported by Paul including complement binding, binding to FcγR1 and induction in response to viral stimulation. However, should there be any doubt as to the equivalence relationships between mouse and human isotypes, the equivalences are stated more explicitly by Hussain, *Clinical Diagnostic Lab. Immunol.* 2, 726-732 (1995) at p. 729, second column, second paragraph, which equates murine IgG2a and IgG2b with human IgG1 and IgG3, murine IgG1 with human IgG4 and murine IgG3 with human IgG2. (Cite no. 1092, cited in Supplemental IDS submitted on 08/07/2008.) In similar vein, Clark, *Chem. Immunol.* 65:88-110 (1997) reports that "human IgG4 is the only human IgG subclass

which does not activate complement and the subclasses IgG1 and 3 are most effective [citations omitted]. (Cite no. 1091, cited in Supplemental IDS submitted on 08/07/2008.) For mouse it is the subclasses IgG2a and IgG2b which are active with IgG1 and possibly IgG3 being inactive" (see pp. 7-8 of attached preprint). Because mouse IgG1 is most similar in properties to human IgG4, not human IgG1, an artisan following the Examiner's line of reasoning would have been led to produce a humanized antibody with human IgG4 isotype. Thus, the cited combination of references teaches away from the claimed invention.

Applicant also disagrees with the Examiner's position that the artisan would have immediately known from Majocha that antibodies cross the blood brain barrier in sufficient amounts to have a useful therapeutic effect. Majocha provides no evidence to show passage of antibodies across the blood brain barrier. Moreover, this view is contrast to other references of record, not least Marcell Morrison-Bogorad (excerpted above) or Walker who reports that the "blood-brain barrier prevents the passage of many types of molecules from the bloodstream to the brain . . . rendering vascular delivery of ligands to Aβ problematic" (at p. 377, first column, first paragraph) reference. As with Becker, the Examiner appears to be considering Majocha not from the perspective of the skilled person not knowing whether the methods discussed in the references would be successful in treatment or diagnosis of Alzheimer's disease, but instead from an artificial perspective in which it is presumed that the methods had worked and all unpredictability is removed. As discussed above, MPEP 2121 does not support any such presumption in the present circumstances."

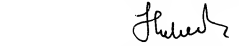
For these reasons, it is maintained that the combination of references taught away from the claimed invention, and did not provide a reasonable expectation of success.

¶¶23-27. All of the remaining art rejections are also premised on the allegation that the combination of Kuby and Adair would have rendered obvious the selection of a human IgG1 isotype in the claimed methods. The distinctions discussed above are thus equally applicable.

¶28. Claims 1-2, 4, 6-8, 10-12, 17, 21-24, 31-32, 35-37, 82-90 and 93-104 stand provisionally rejected over 11/520,438. MPEP 804 provides that if provisional obviousness-type double patenting rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. Here, the present application has an earlier filing date than the cited application. Accordingly, if the present application is allowed first, it is requested the rejection be withdrawn per MPEP 804. If the cited application is allowed first and the claims in the present and cited applications remain in their current form, applicant will consider filing a terminal disclaimer.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Joe Liebeschuetz
Reg. No. 37,505

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
JOL:sjj:vtt
61458741 v1